REMARKS

Applicant wishes to thank the Examiner for courtesies extended during the telephonic interview conducted on April 6, 2004. The interview concerned discussion of the Office Action of January 28, 2004. In particular, the discussion concerned enablement of the claims with regard to autoimmune disease and cancer. The Examiner's suggestions have been incorporated into the current Amendment.

With this amendment, claims 1-3, 5, 7, 11, and 20 are the claims currently being examined. Claims 1 is the only claim currently being examined which is in independent form. Claim 20 is hereby cancelled. It is submitted that no new matter has been added to this application by way of this amendment.

Remarks Directed to Rejection of Claim 20 under 35 U.S.C. §101

Claim 20 stands rejected because recitation of a use, without setting forth any steps involved in the process, results in ... a claim which is not a proper process claim under 35 U.S.C. §101. (Office Action, January 28, 2004, p.3, section 4)

Applicant hereby cancels claim 20 and therefore requests withdrawal of this rejection.

Remarks Directed to Rejection of Claims 1-3, 5, 7, 11, and 20 under 35 U.S.C. §112, First Paragraph

Claims 1-3, 5, 7, 11, and 20 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention. Specifically, the claims appear to have been rejected following consideration of several factors relevant to enablement as outlined in In re Wands (858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Metes and bounds of the promoter 'region'

The Examiner has rejected the claims as not enabled since they are "drawn to haplotyping in a 'region' wherein the specification does not define the metes and bounds of said region." However, the specification does indicate that the FasL promoter 'region' is 1065 nucleotide long and extends "from position -1032 to +33." (p.14, lines 9-10 and p. 17,

lines 14-15) Further, the application discloses that the numbering system used to designate the promoter region and particular nucleotide identities within the promoter region is an art recognized numbering system. The specification states that the "5' promoter region sequence of the Fas ligand [is] known" and cites C. J. Holtz-Heppelmann et al., J. Biol. Chem. 1998, 273(8):4416-4423. (p. 40, lines 2-5)

Thus, Applicant submits that the specification does define the metes and bounds of the indicated 'region." An amendment to claim 1 includes the information that the haplotyping is performed in a Fas ligand promoter region extending from nucleotide –1032 to nucleotide +33 in order to clarify the claim. Applicant therefore requests withdrawal of this rejection of the claims under 35 U.S.C. §112, first paragraph.

Diagnostic for susceptibility to disease

The Examiner holds that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). (MPEP 2164.01)

Applicant submits that the claims are fully enabled since, as described below, no undue experimentation is necessary to practice the invention. Applicant therefore requests withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph.

Claims Directed to a Diagnostic for Susceptibility to Disease, Not Correlation with Disease

The Examiner asserts that undue experimentation is necessary to practice the present invention because no predictable correlation can be made between polymorphisms and any phenotypic trait, such as a disease state or a physiological state. (Office Action, January 28, 2004, p.6)

Applicant notes that the claims are not directed to a predictable correlation between polymorphisms and any phenotypic trait, such as a disease state or a physiological state, as the Examiner states. Rather, the claims being currently examined are directed to a diagnostic

based on a relationship between particular polymorphisms and susceptibility to a disease state. This fact is apparent in independent claim 1 which explicitly uses the term "susceptibility." Further, the specification indicates the discovery of "single nucleotide polymorphisms... [in] Fas ligand promoter sequences which are independent indicators for disease susceptibility." (p.1 lines 7-9, emphasis added)

Given this multifactorial nature of immune diseases, it would be recognized by one of skill in the art that a change in FasL expression, while conferring susceptibility to immune disorder, may also manifest in various ways, such that a particular phenotype may or may not be apparent. Thus, a particular polymorphism in the FasL promoter, may, in combination with environmental factors or other genetic factors, affect immune function to produce various disease phenotypes. While a particular FasL promoter polymorphism affecting FasL expression may or may not be diagnostic for disease, the same polymorphism is diagnostic for susceptibility to disease, as detailed in the specification.

Applicant submits that the claims, directed to a diagnostic method for determining autoimmune disease or cancer susceptibility are fully enabled, as described in more detail below. Applicant therefore requests withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph.

Fas Ligand Implicated in Disease – State of Prior Art and Predictability

The examiner rejects the claims as not enabled because it is unpredictable in the art whether a particular polymorphism is associated with a disease state. The state of the prior art is a factor in determining whether undue experimentation is required.

Applicant again emphasizes that the claims are drawn to susceptibility, not disease. Applicant further submits that the state of the prior art at the time of filing was such that one of skill in the art would have recognized that the Fas/FasL system is important in control of the immune system, and dysregulation of the Fas/FasL system is a factor in disease, and in particular, in autoimmune disease and cancer.

Further, Applicant submits that this is apparent from the teachings of the specification. For example, the specification states that "The critical role of the FasL and Fas interaction in the maintenance of immune tolerance and prevention of autoimmune disease has been demonstrated by the finding that mutations of Fas or FasL genes lead to autoimmune disease in lpr/lpr and gld/gld mice, respectively (R. Watanabe-Fukunaga et al.,

Nature 1992, 356(6367):314-7; T. Takahashi et al., *Cell* 1994, 76(6):969-76). Human autoimmune lymphoproliferative syndrome (ALPS or Canale-Smith Syndrome) characterized by defective lymphocyte apoptosis, lymphocyte accumulation, and humoral autoimmunity has been found to be associated with inherited mutations in the Fas (J. Drappa et al., *N. Engl. J. Med.* 1996, 335(22):1643-9; G.H. Fisher et al., *Cell* 1995, 81(6):935-46; F. Rieux-Laucat et al., *Science* 1995, 268(5215):1347-9; M.C. Sneller et al., *Blood* 1997, 89(4):1341-8; M.C. Sneller et al., *J. Clin. Invest.* 1992, 90(2):334-41). FasL gene mutation has also been implicated with SLE in one patient (J. Wu et al., *J. Clin. Invest.* 1996, 98(5):1107-13). These findings stress the importance of Fas and FasL interaction in the maintenance of immune tolerance and prevention of autoimmune disease in humans." (p.4, line 24 - p.5, lines 1-16)

Thus, Applicant submits that given the teachings in the specification demonstrating the state of the prior art, one of skill in the art would have recognized the discovery of FasL promoter polymorphisms, and especially polymorphisms affecting promoter activity, as enabling the claims regarding a diagnostic for susceptibility to autoimmune disease since no undue experimentation would be necessary to practice the invention.

Further, the specification provides evidence that polymorphisms in the FasL promoter occur at transcription factor binding sites and that polymorphisms in the FasL promoter affect FasL expression. In particular, the present specification teaches that the –844 polymorphism which is the subject of the claims under current examination is present in a transcription factor binding site in the FasL promoter region and that the identity of the nucleotide at the –844 polymorphism affects promoter activity.

Given the teachings of the specification showing that one of skill in the art would recognize that FasL is intimately involved in immune system regulation, combined with the teaching of polymorphisms and their effect on promoter activity, Applicant submits that one of skill in the art would recognize that polymorphisms affecting promoter activity, and transcription factor binding, would affect immune function and that identity of the nucleotide present at the polymorphism would be thus recognized as a susceptibility factor for autoimmune disease. Thus Applicant submits that no undue experimentation is necessary to practice the invention and the claims are therefore enabled. Applicant therefore requests withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph.

The amount of direction provided by the inventor and the existence of working examples

The Examiner finds that the claims are not enabled because the specification does not predictably establish a correlation with "any autoimmune disease or cancer in general, or even any specific autoimmune disease or cancer." (p.7-8) However, no undue experimentation is required where the specification provides sufficient direction and working examples.

Applicant again emphasizes that the claims are directed to a diagnostic of susceptibility to disease and submits that the present specification contains sufficient direction and working examples such that no undue experimentation is necessary to practice the invention. In particular, the specification teaches that the identity of the nucleotide present at a polymorphism is present in a transcription factor binding site, that identity of the nucleotide present at a polymorphism affects transcription factor binding and promoter activity. Further, the specification details that identity of the nucleotide present at polymorphism –844 correlates with diagnosis of SLE, and specifically with presence of a "T" at nucleotide –844 in the FasL promoter. For example, Table 1 shows presence of T at position –844 in 56% of SLE patients and only 36% of normal control patients. As set forth in the inventor's Declaration, submitted herewith, this finding is statistically significant. In addition, the specification states that "TAAG and TGAG haplotypes of a Fas ligand promoter at positions –844, -756, -478 and –205, respectively are associated with individuals suffering from SLE in greater than 90% of a diagnosed disease group." (p.20, lines 18-20) Thus, Applicant submits that the specification does teach correlation of identity of the nucleotide present at a polymorphism with an effect on transcription factor binding and promoter activity, and further, with susceptibility to a particular autoimmune disease, SLE.

Applicant further submits that one of skill in the art would recognize that correlation of the identity of a particular FasL promoter polymorphism with SLE is indicative of correlation with susceptibility to autoimmune diseases generally. SLE is considered by those of skill in the art to be the "prototypic" autoimmune disease. This fact is taught in the specification which states that SLE is "considered a prototypic systemic autoimmune disease." (p.6, line 12, emphasis added) In other words, one of skill in the art would recognize that correlation of SLE with a particular susceptibility factor is indicative of a

susceptibility factor for autoimmune disorders generally, including disorders such as "systemic vasculitis, autoimmune lymphoproliferative syndrome, glomerulonephritides, Sjogren's syndrome and IgA nephropathy." (p.21, lines 7-9) These statements must be taken as true by the Examiner unless the Examiner finds there is reasonable doubt regarding this assertion. (MPEP 2164.04) Taken together, the state of the prior art with regard to the role of the Fas/FasL system in the immune system, and the association of a FasL polymorphism with SLE, Applicant submits that one of skill in the art would recognize that a claim to a diagnostic for susceptibility to autoimmune disease generally is enabled. Further, Applicant submits evidence in the form of a Declaration by the inventor citing several representative references in major scientific journals which state explicitly that SLE is a prototypic autoimmune disease. Thus, Applicant submits that the teachings of the specification provide sufficient direction and working examples of correlation between such that no undue experimentation is necessary to practice the invention Applicant therefore requests withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph.

Fas Ligand Implicated in Cancer – State of Prior Art

The Examiner finds that the claims are not enabled because the specification does not predictably establish a correlation with "any autoimmune disease or cancer in general, or even any specific autoimmune disease or cancer." (p.7-8)

Applicant again emphasizes that the claims are directed to a diagnostic of susceptibility to disease and submits that the present specification contains sufficient direction and working examples such that no undue experimentation is necessary to practice the invention regarding a diagnostic for susceptibility to cancer. In particular, Applicant submits that one of skill in the art would recognize, given the teaching in the specification, that a polymorphism in the FasL promoter is a factor in susceptibility of an individual to cancer. As detailed in the specification, FasL is known to be present in numerous types of cancers, including human melanoma, hepatocellular carcinoma, lung cancer, astrocytoma, esophageal carcinoma, gastric adenocarcinomas, ovarian carcinoma, and colon adenocarcinomas. The Examiner discounts these facts stating that "such teaching is not an indication that Fas ligand is necessarily involved in cancer, because many genes and proteins are expressed in cancer without being directly or indirectly involved in such." (p.6)

However, the teaching of the specification is not limited to the observation that FasL is expressed in many types of cancers. As further detailed in the specification, "Recent evidence suggests that tumor-infiltrating lymphocytes (TILs) are susceptible to Fas-mediated counterattack.." This statement indicates that the prior art at the time of filing recognized that aggressivity and tendency to metastasis in cancer cells may be mediated by FasL expression by tumor cells. In other words, the tumor cells evade the immune cells by inducing apoptosis therein. As stated in the specification "[i]n esophageal cancer, the extent of apoptosis of TILs was found to vary regionally within the tumors in relation to the local status of FasL expression, local expression of FasL by nests of tumor cells was associated with apoptotic depletion of TILs. M.W. Bennett et al., *J. Immunol* 1998, 160(11):5669-75. In addition to local defense, FasL expression facilitate the establishment of tumor metastases in tissues such as the liver, where the indigenous normal cells are themselves sensitive to FasL. K. Shiraki et al., *Proc. Natl. Acad. Sci. U.S.A.* 1997, 94(12):6420-5. Significant correlation between tumorigenicity and expression of FasL has raised the possibility that FasL may be a useful diagnostic marker for malignant melanomas. A. Maeda et al., *Br. J. Dermatol.* 1998, 139(2):198-206." In addition, the specification teaches that "[i]t has recently been established that colon cancers typically express FasL, a potent mediator of immune privilege. Expression of FasL potentially enables colon tumors to counterattack Fas-sensitive anti-tumor immune effector cells by delivering a Fas-mediated apoptotic death signal. J. O'Connell et al., *J. Pathol.* 1998, 186(3):240-6.

Further, the specification details that the "liver is the most common site for development of metastatic colorectal cancer. The remarkably high incidence of liver metastases in patients with colorectal cancer suggests that the liver provides an environment conducive to the development of metastasis. It has been demonstrated that FasL expressing colon cancer cells promoted local tumor growth by inducing apoptotic cell death in normal heptocytes at the tumor margin in colorectal hepatic metastasis (K.F. Yoong et al., *Am. J. Pathol.* 1999, 154(3):693-703)."

While a FasL promoter polymorphism may not be found in every individual having cancer, where a polymorphism is found one of skill in the art would recognize the specification as teaching that the polymorphisms are associated with FasL expression changes. FasL expression by a tumor cell is an indication of tumor aggressivity, while a FasL

promoter polymorphism in an individual having a tumor is an indication of altered immune response, and is therefore an indicator of susceptibility of the individual to cancer growth and metastasis.

Applicant submits that this material, present in the specification, clearly outlines the relation of the Fas/FasL system to cancer, and that one of skill in the art would have understood from this that a polymorphism in the FasL promoter would implicate disease associated with the immune system, such as cancer. Applicant further submits that since one of skill in the art would have understood the relationship between the discoveries of the present invention and the knowledge in the prior art, the claimed diagnostic methods for susceptibility to cancer require no undue experimentation and are therefore fully enabled. Applicant therefore requests withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph.

Specific polymorphisms and transcription factor binding

It is asserted that the specification does not teach any specific haplotypes that contain polymorphisms that bind NF-IL6 transcription factor. Specifically, it is asserted that "[w]hile the specification does teach a luciferase assay with regard to different a T and a C at position –844 and that the C allele showed almost twice the activity than the T allele, the specification does not teach how such is correlated to binding of NF-IL6 ..." (Office Action, January 28, 2004, p.5)

However, the specification does clearly teach specific haplotypes that contain polymorphisms that bind NF-IL6 transcription factor. For example, the specification teaches that "[t]he SNP at nt -844 is within the C/EBPβ (NF-IL6) transcription factor and that different alleles of the C/EBPβ element have different affinities for the transcription factor." (p.35, lines 11-13) Further, in describing the EMSA analysis shown in Figure 2B the specification teaches that "[t]aken together, the putative C/EBPβ region including -844 is indeed a C/EBPβ element, different genotypes of FasL promoter have [the] dramatic[ally] different affinities for the C/EBPβ." (p.28, lines 12-14)

Applicant submits that the data discussed above, as well as data further detailed in the specification, teach specific sequences that contain polymorphisms that bind NF-IL6

transcription factor. Applicant therefore requests withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph.

Table 5 and the term 'putative'

It is asserted that Fig. 5 shows "putative" haplotypes for SNPs of the FasL promoter and that the use of the word "putative" makes it unclear as to how such data was obtained. Applicant submits the inventor's Declaration herewith, explaining the art recognized use of this term. Applicant submits that the claims are enabled and the term "putative" does not render an association between susceptibility to disease and FasL polymorphisms unpredictable. Applicant therefore requests withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph.

Remarks Directed to Rejection of Claims 1-3, 5, 7, 11, and 20 under 35 U.S.C. §112, Second Paragraph

Claim 1 is rejected as indefinite as the final process step does not relate back to the preamble of the claim. The claim has been amended to relate back to the preamble as required. Applicant therefore requests withdrawal of this rejection under 35 U.S.C. §112, second paragraph.

Claim 1 is rejected as indefinite because "neither the specification nor the claims define the requisite degree encompassed by the term "region." However, the specification does indicate that the FasL promoter 'region' is 1065 nucleotide long and extends "from position -1032 to +33." (p.14, lines 9-10 and p. 17, lines 14-15) Further, the application discloses that the numbering system used to designate the promoter region and particular nucleotide identities within the promoter region is an art recognized numbering system. The specification states that the "5' promoter region sequence of the Fas ligand [is] known" and cites C. J. Holtz-Heppelmann et al., J. Biol. Chem. 1998, 273(8):4416-4423. (p. 40, lines 2-5) Thus, Applicant submits that the specification does define the metes and bounds of the indicated 'region." An amendment to claim 1 includes the information that the haplotyping is performed in a Fas ligand promoter region extending from nucleotide –1032 to nucleotide +33 in order to clarify the claim. Applicant therefore requests withdrawal of this rejection under 35 U.S.C. §112, second paragraph.

Claims 2, 3, 5 and 20 are rejected under 35 U.S.C. §112, second paragraph for reciting the term "polymorph." The Examiner holds that the claims should be amended to replace the term "polymorph" with the term "polymorphism," in order "to agree with the current English designation for the term." Applicant has amended claims 2, 3 and 5 to comply with the Examiner's request and clarify the claim. Claim 20 has been canceled, so the rejection is moot. Applicant therefore requests withdrawal of this rejection under 35 U.S.C. §112, second paragraph.

Claims 7 and 11 are rejected under 35 U.S.C. §112, second paragraph as lacking sufficient antecedent basis for the term "nucleotide site." The claims have been amended such that antecedent basis is proper. Applicant therefore requests withdrawal of this rejection under 35 U.S.C. §112, second paragraph.

Claim 20 is rejected under 35 U.S.C. §112, second paragraph as indefinite. As this claim has been canceled, Applicant submits that the rejection is now moot and therefore requests withdrawal of the rejection.

Summary

Claims 1-3, 5, 7, and 11 are the claims currently being examined in this application. Each claim is believed to be in proper form and directed to allowable and patentable subject matter. Reconsideration and allowance of the claims is requested.

Respectfully submitted,

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